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Biochemical Evaluation of Trigonella Foenum-Graecum Seed Extract in Metabolic Syndrome

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ABSTRACT

Background: Metabolic syndrome is a crucial factor in causation of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD). Fenugreek seeds have beneficial effects on improvement of metabolic syndrome.
Objective: Evaluation preventive and curative efficacy of aqueous extract of fenugreek seeds in metabolic syndrome by observation of biochemical parameters and its correlation.
Methods: Case control study consisting of controls (n=34) and subjects (n=34) with metabolic syndrome. Case group was administered aqueous extract of fenugreek seeds equivalent to 13.2gm powder/day for 3 months. Both groups were evaluated at base line and after three months while status quo was maintained. Subjects were advised not to alter their lifestyle.
Results: After three months of adjunct therapy, there was significantly improvement in glycaemic status, insulin resistance, HOMA, and antioxidant superoxide dismutase (SOD) in metabolic syndrome when compared with control group.
Conclusion: Aqueous extract of fenugreek seeds is effective and safe to control glycaemic, insulin resistance, dyslipidaemias and antioxidant status in metabolic syndrome.

Key Words: Fenugreek, metabolic syndrome, HbA1c, HOMA, SOD.

INTRODUCTION

Metabolic syndrome is a crucial factor in causation of type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD). Rapid nutritional and lifestyle transition along with genetic factors are prime reasons for increasing prevalence of obesity and metabolic syndrome in urbanized areas of South Asia which is reaching epidemic proportions. [1] The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. [2] The development of obesity in metabolic syndrome seems to be an important factor portending the development of insulin resistance, which in the presence of a genetically determined propensity to beta-cell dysfunction results in alterations in glucose tolerance. It is an important determinant of insulin sensitivity [3] Body-fat distribution and dietary constituents have also been shown to modulate insulin sensitivity. Peripheral insulin resistance and hyperinsulinemia have been proposed to impair insulin-mediated renal sodium resorption, which may contribute to hypertension. [4] Metabolic syndrome is also related to age, with aging being associated with a decline in the body's responsiveness to carbohydrates. [3] Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells. [5]

In diabetes, there is an imbalance in the metabolism of lipids and fat, which leads to abnormal serum lipid pattern. Of the various serum lipids, there is ample evidence for a strong association for cholesterol. Recent studies reveal small-dense low density lipoprotein (LDL) to be more susceptible to oxidation. Oxidized LDL enhances foam cell formation and this leads to inflammatory and thrombogenic processes. Small-dense LDL levels have high triglyceride (TG) levels and low levels of high density lipoprotein (HDL). A recent study showed that migrant Asian Indians have an excess of small-dense LDL molecules, this might be one of the mechanisms contributing to increase in CHD and diabetes in Indians. In contrast to LDL cholesterol, HDL cholesterol actually plays a protective role, as it is both antiatherogenic and also prevents peroxidation as it carries enzymes like paraoxonases. [4, 6, 7]

There is an overwhelming moral, medical and economic imperative to identify metabolic syndrome, so that lifestyle interventions and treatment may prevent the development of diabetes and/or cardiovascular disease. International Diabetes Federation (IDF) definition of metabolic syndrome while addressing both clinical and research needs; provides an accessible diagnostic tool suitable for worldwide use, especially due to modifications applied for ethnicity. [8]

Plants have played a significant role in maintaining human health and improving the quality of life for thousands of years. According to the World Health Organisation (WHO), about three quarters of the world's population relies on traditional medicine for primary health care needs and most of this treatment involves the use of plant extracts or their active components. [2, 9] Fenugreek has been extensively used in alternate medicine for treatment of diabetes. Its properties were evaluated by modern researchers. It was reported to have action to correct insulin resistance, a basic etiological factor for development of type 2 diabetes or cardiovascular disorders along with antilipidemic properties. [10-14]

We therefore undertook this study considering scope of fenugreek as low-risk, inexpensive, food-based intervention aimed at normalizing metabolic milieu in high risk population. Fenugreek seed aqueous extract in tablet form was used. We have studied biochemical parameters- fasting glucose, HbA1c, HOMA 2 [5,15] and lipid profile. Due consideration was also given to anthropometric (waist circumference, weight, BMI) and safety parameters (Haemoglobin % and liver function tests).

MATERIALS AND METHODS

Randomized case control study was undertaken in Department of Biochemistry, Grant medical college and Sir J. J. groups of Hospitals, Mumbai in 34 control and 34 subjects of metabolic syndrome with age (30 to 60 years) and sex matched. Patients received adjunct therapy of 1.32gm/day aqueous extract of fenugreek seeds for 3 months. Initially small doses were given to the patients as adjunct therapy and doses were increased slowly with careful monitoring for side effects including risk of hypoglycaemia for 3 months. Approval of the ethical committee of the institute was obtained for the study. Informed consent was taken from the subjects. Subjects with serious hepatic or renal impairment, diabetes, cardiovascular co–morbidities, psychiatric disorders, human immuno-deficiency virus infection, pregnancy, addicts i.e. drugs, alcohol and tobacco were excluded from studies. Metabolic syndrome subjects were selected based on following factors:

1) Central obesity (as measured by waist circumference), South Asians (Asian-Indian population) Male ≥ 90 cm. Female ≥ 80 cm

2) Any two of the following four factors:

• Raised TG level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality

• Reduced HDL cholesterol :< 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL

(1.29 mmol/L) in females, or specific treatment for this lipid abnormality

• Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension

• Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L)

Baseline and 3 months follow up study was done for glucose, insulin, C-peptide, MDA, SOD, lipid profile, haemoglobin, alanine transaminase (ALT) and renal function tests which were estimated using chemiluminescence (Immulite 1000), fully automated chemistry analyser (Olympus AU-400) and spectrophotometer (Jasco-V670).Clinical history, blood pressure, anthropometric measurements - height, weight, hip and waist measurements, BMI was also measured. [9]

Homeostatic model (HOMA 2) is a method for assessing β – cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C- peptide concentrations. HOMA2, the correctly solved computer model, has nonlinear solutions. [4, 5]

Plant extract:

Aqua soluble extract of fenugreek tablets were supplied by FDA approved ayurvedic manufacturer Sheetal Medicare. Fenugreek seeds purchased from local market were certified by botanist. Material was tested and certified as per Agmark standards for pesticides, fertilizers, toxins and heavy metals residues. Seeds were washed, dried, powered and decoction was prepared from which tablets were made by the standard procedure in text book of Indian medicine, 'SharangdharSamhita'. [16] Aqueous extract of Fenugreek was made in 1:10 ratio. Gum Acacia was used as binder and filler. One tablet contained 330 mg extract. 1. 32gm extract was equivalent to 13. 2gm Fenugreek seed powder. Our optimum dose was 4 tablets/day. During the 1st week only 1 tablet/day was administered 5-10 minutes before breakfast. In the 2nd week, 2 tablets/day were given each before breakfast and dinner. The dosage was further increased in the 3rd week with a total of 4 tablets/day, 2 tablets before breakfast and 2 tablets before dinner.

Statistical analysis: Statistical analysis (Mean and Standard Deviation) was done using Mini-tab 17 software with 95% confidence interval.

RESULTS

Table 1: Anthropometric parameters in control and metabolic syndrome

Anthropometric Parameters	Control Mean ± SD	Metabolic Syndrome Mean ± SD
Age (Years)	43.24 ± 10.32	43.27 ± 10.26
Weight (kg) Baseline	72.77 ± 9.37	73.00 ± 8.05
Weight (kg) After 3 months	72.77 ± 8.56	69.41 ± 7.77
BMI Baseline	27.26 ± 3.67	27.50 ± 3.22
BMI After 3 months	27.25 ± 3.47	25.92 ± 3.48
Waist/Hip ratio Baseline	0.87 ± 0.03	0.87 ± 0.03
Waist/Hip ratio After 3 months	0.87 ± 0.03	0.82 ± 0.03

Table 2: Biochemical parameters in control and metabolic syndrome

Biochemical Parameters	Control Mean ± SD	Metabolic Syndrome Mean ± SD
Fasting Glucose Baseline	99.97 ± 3.91	105.21 ± 3.98
Fasting Glucose After 1 month	-----	87.47 ± 4.55
Fasting Glucose After 3 months	98.4 ± 5.16	76.94 ± 4.08
Insulin Baseline	19.65 ± 9.22	21.41 ± 17.68
Insulin After 3 months	18.82 ± 7.00	14.72 ± 6.30
HOMA IR2 Baseline	2.53 ± 1.1	2.45 ± 0.92
HOMA IR2 After 3 months	2.56 ± 0.8	1.8 ± 0.73
C-peptide Baseline	3.06 ± 1.2	3.17 ± 1.54
C-peptide After 3 months	3.04 ± 1.01	2.68 ± 1.15
HbA1C Baseline	5.17 ± 0.75	5.68 ± 0.59
HbA1C After 3 months	5.2 ± 0.73	5.03 ± 0.67
Total Cholesterol Baseline	225.2 ± 13.82	227.26 ± 15.53
Total Cholesterol After 3 months	227.87 ± 13.35	194.26 ± 13.07
Triglyceride Baseline	173.13 ± 9.81	180.65 ± 11.08
Triglyceride After 3 months	175.53 ± 11.49	145.65 ± 11.45
HDL Baseline	39.00 ± 3.54	35.26 ± 1.75
HDL After 3 months	39.33 ± 3.06	47.79 ± 1.7
LDL Baseline	157.98 ± 13.53	160.48 ± 16.44
LDL After 3 months	160.48 ± 12.92	131.07 ± 14.27
MDA Baseline	4.28 ± 0.49	5.98 ± 0.9
MDA After 3 months	-----	4.13 ± 0.42
SOD Baseline	826 ± 62.23	627.7 ± 96.64
SOD After 3 months	-----	811 ± 86.11

Table 3: Safety parameters in Control and Metabolic syndrome

Safety Parameters	Control Mean ± SD	Metabolic Syndrome Mean ± SD
Hemoglobin % Baseline	13.85 ± 1.41	13.68 ± 1.41
Hemoglobin % After 3 months	13.92 ± 1.23	13.79 ± 1.42
Urea Baseline	21.23 ± 4.99	20.91 ± 4.96
Urea After 3 months	19.20 ± 2.80	19.29 ± 3.31
Creatinine Baseline	0.80 ± 0.12	0.78 ± 0.11
Creatinine After 3 months	0.90 ± 0.13	0.94 ± 0.12
ALT Baseline	20.33 ± 7.25	26.53 ± 4.82
ALT After 3 months	20.67 ± 8.31	25.65 ± 4.70

DISCUSSION

Our study is especially focussed on subjects of metabolic syndrome. These subjects manifest abnormalities of glucose

and lipid metabolism. Fenugreek was reported earlier to have spectrum of pharmaceutical properties that can correct metabolic defects (especially insulin resistance and dyslipidemias) associated with diabetes. [10-13] However these studies had several limitations as assessed for methodological quality of randomized controlled trials using the Jadad scale. [14] These studies were mostly non-controlled, carried out on small number of subjects and only few biochemical parameters were studied. These were done before new IDF definition of metabolic syndrome was published. We are comparing our findings broadly on the basis of action of the fenugreek seeds.

The poor acceptability of fenugreek seeds due to its bitter taste, poses a problem. Most subjects were unwilling to compromise type of food and its flavour and were reluctant to change their food habits i.e. replace their favourite food mixed with seed powder as used by earlier investigators. They were also reluctant to take sticky paste of 7-8gm seed powder twice a day for many weeks. Gupta et al. 2001 have used hydro-alcoholic extract of fenugreek in capsule form. Fenugreek in tablet form was quite acceptable and convenient in subjects. [10] Tablet form ensured adequate dose. Subjects were advised to continue similar lifestyle and food habits during study period. Our study has confirmed that aqueous extract prepared by simple yet standard Ayurvedic procedure with specified binding retains medicinal properties of fenugreek.

Table 2 shows significant improvement among baseline and after 3 months fasting glycaemic status, lipid profile, oxidative stress and SOD levels in metabolic syndrome group. This is due to improved insulin sensitivity as measured by HOMA IR 2 model. These findings are similar with Sharma et al. 1999 and Gupta et al. 2001. [10, 11] Levels of C- peptide were also reduced. Our findings correlate well with Maleppillil et al.2005, who have demonstrated that a dialyzed aqueous extract of fenugreek seeds possesses hypoglycaemic properties and that it stimulates insulin signalling pathways in adipocytes and liver cells in-vitro models. Fenugreek induces a rapid, dose dependent stimulatory effect on cellular glucose uptake by activating cellular responses that lead to glucose transporter (GLUT4) translocation from intracellular space to the cell surface. Their results also indicated that fenugreek contains factor(s) that might act independently of insulin to enhance glucose transporter-mediated glucose uptake. [9] Apart from these effects at cellular level, fenugreek also acts on organ level. It delays gastric emptying and interference with glucose absorption. This is attributed to high fibre content, inhibition of pancreatic c-amylase and intestinal disaccharidase enzymes, and due to the presence of orally active principles (alkaloids, flavonoids, glycosides, steroids, amino acids and minerals). Since we have used aqueous extract, our results are similar to those retaining actual properties of fenugreek. The compound 4-hydroxyisoleucine, which represents up to 80% of free amino acids in fenugreek seeds, was found to possess insulin β-secretagogue properties both in pancreatic islets in-vitro and in rats and dogs in-vivo. [13,18]

Our lipid profile level results correlate well with others. [7,11,12,14,15] These effects may be due to sapogenins, which increase biliary cholesterol excretion, in turn leading to lowered serum cholesterol levels. The lipid-lowering effect of fenugreek might also be attributed to its estrogenic constituent, indirectly increasing thyroid hormone T4. [12,15,17,18]

Anthropometric study matches with Misra A et al. 2007, Deepa R et al. 2002 and Mohan V 2001. [1,4,20] We all agree that Asian Indians have greater degree of central obesity despite lower BMI. Table 1 indicates improvement in weight, BMI and waist circumference, in study group. [11,12] International expert panel: National Cholesterol Education Program (NCEP) adult treatment panel III report has encouraged use of plant stanols/sterols and

viscous (soluble) fibre as therapeutic dietary options due to nutritional benefits to enhance lowering of LDL cholesterol. In this modern era, many studies have elaborated the relevant use of herbal medicines on scope and potential of fenugreek for drug development in diabetes. **[13,19,21-24]**

CONCLUSION

Our findings support for potential of fenugreek as excellent therapeutic option in management of metabolic syndrome. In addition to antiglycemic and antilipidemic properties, anti-inflammatory, antioxidant and antiplatelet activities of aqueous extract of fenugreek are beneficial.

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